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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/899,634 | 07/05/2001 | Thomas Buhler | 4-31499A | 5159 |

1095 7590 08/26/2003

THOMAS HOXIE
NOVARTIS, CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 430/2
EAST HANOVER, NJ 07936-1080

| EXAMINER |
|---|
| SULLIVAN, DANIEL M |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1636 | 16 |

DATE MAILED: 08/26/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/899,634 | BUHLER ET AL. | |
| | Examiner | Art Unit | |
| | Daniel M Sullivan | 1636 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *17 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *1,2 and 11-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

This is the First Office Action on the Merits of the application filed 5 July 2001, which claims benefit of U.K. patent application 0016791.6 filed 7 July 2000.

### *Election/Restrictions*

Applicant's election with traverse of Group II (claims 3-10) in Paper No. 15, filed 17 June 2003, is acknowledged. The traversal is on two grounds. First, Applicant argues that restriction is unwarranted because the Groups set forth in the restriction requirement are not both independent and distinct. This argument has been fully considered but is not found persuasive because the MPEP makes clear that restriction of dependent, or related, inventions is proper if the inventions are distinct, "[t]he law has long been established that dependent inventions (frequently termed related inventions)...may be properly divided if they are, in fact, 'distinct' inventions, even though dependent" (MPEP §802.01). The previous Office Action clearly sets forth why the named inventions, while related, are distinct. Applicant's arguments are limited to reasons why the Inventions are related, which is acknowledged, but do not address the grounds for distinctness.

Applicant next argues that examining all of the Inventions in a single application does not impose a serious burden on the examiner because the search and examination of the groups would substantially overlap. This argument has been considered but is not found persuasive because, for reasons set forth in the previous office action, each of the Inventions are directed to distinct subject matter. Therefore the Inventions cannot be searched and examined coextensively and each Invention imposes an additional burden on the examiner.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1, 2 and 11-25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Invention.

***Claim Objections***

Claims 3, 4, 6, 7, 9 and 10 are objected to because of the following informalities:

Claims 3, 4, 6, 7, 9 and 10 depend from a non-elected base claim. This objection can be overcome by the appropriate incorporation of the limitations of claims 1 or 2 into claims 3, 4, 6 and 7.

Claim 3 is additionally objected to for using an undefined abbreviation. Each abbreviation should be accompanied by a definition the first time the abbreviation is used in the claims.

Claim 10 is additionally objected to because the word "been" is misspelled.

Appropriate correction is required.

***Claim Rejections - 35 USC § 101***

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 3 and 4 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims are directed to a DNA sequence encoding a C-terminally truncated porcine CAR. Because mutations producing a C-terminally truncated protein can occur in nature, the claims encompass products that occur naturally absent the hand

of man. This rejection can be overcome by amending the claims to clearly indicate the hand of man such as by limiting the claimed subject matter to an isolated DNA sequence.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

*Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

The claims are directed to a DNA sequence which encodes fragments, including C-terminal truncations, or variants of a porcine CAR, wherein said fragments or variants have the function of mediating adenoviral transduction. Claims are also directed to vectors and host cells

comprising said DNA sequence. "Fragment" is defined on page 5 of the specification as "a polypeptide sequence that is shorter than the reference sequence but that retains essentially the same biological function or activity as the reference polypeptide". Variant is defined in the paragraph bridging pages 5 and 6 of the specification as "a polypeptide that differs from a reference polypeptide, but retains the essential properties thereof." Therefore, to the extent that they are directed to nucleic acids encoding fragments of a porcine CAR, the claims encompass a genus of nucleic acids encoding any and all fragments of a porcine CAR which retain the ability to mediate adenoviral transduction. With regard to variants, because the specification places no limitation on the type or degree of modification of the reference sequence, the claims are generic to essentially any nucleic acid encoding a polypeptide which mediates adenoviral transduction regardless of the structure of said polypeptide.

The Guidelines for Written Description state: "when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus" (Federal Register, Vol. 66, No. 4, Column 2, page 71436). "The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus... See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406" (MPEP §2163(3)(a)(ii)).

With regard to reduction to practice, the instant disclosure provides a single example of a fragment a porcine CAR which mediates adenoviral transduction (i.e., the C-terminally truncated polypeptide set forth as SEQ ID NO: 2). In addition, the art provides several variants of porcine CAR which mediate adenoviral transduction (i.e., species homologues; see especially Fechner *et al.* (1999) *Gene Therapy* 6:1520-1535). However, given the breadth of the claimed genus, which encompasses any fragment or any structural variant, the species reduced to practice do not adequately reflect the variation within the claimed genus.

With regard to disclosure of the relevant identifying characteristics, neither the instant disclosure nor the relevant art describe the characteristics of a polypeptide having the function of mediating adenoviral transduction such that the skilled artisan would be able to identify polypeptides encompassed within the structural limitations of the claims which also have the recited function of mediating adenoviral transduction. In fact, as pointed out above, to the extent the claims are directed to variants, the polypeptides encoded by the claimed nucleic acids are unlimited in structure. It is not sufficient to define DNA solely by its principal biological property (i.e., it encodes a polypeptide which mediates adenoviral transduction) because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any DNA with that biological property. Also, naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming all DNA's that achieve a result without defining what means will do is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)).

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed invention commensurate to its scope because it does not provide adequate written description for the broad class of nucleic acids encoding fragments or variants of a porcine CAR which mediates adenoviral transduction. Therefore, only the described nucleic acid encoding the polypeptide set forth as SEQ ID NO: 2 meets the written description provision of 35 U.S.C. §112, first paragraph.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claims 3-10 are additionally rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleic acid encoding the porcine CAR set forth as SEQ ID NO: 2 and fragments thereof, does not reasonably provide enablement for the full scope of variants thereof which mediate adenoviral transduction. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation

needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

*Nature of the invention and breadth of the claims*: The scope of the claims is described herein above. To summarize, the claims encompass nucleic acids encoding any variant of a porcine CAR polypeptide which mediates adenoviral transduction, wherein said variant of a porcine CAR polypeptide is unlimited in structure.

*State of the prior art and level of predictability in the art*: The art teaches that the effect of varying amino acid sequence on the function of a polypeptide is highly unpredictable. For example, Richards (1997) *Cell Mol. Life Sci.* 53:790-802 teaches, "[i]n terms of structural alterations and thermostability, responses to genetic mutations are context dependent and remain difficult to predict with any confidence" (abstract, column 1). Thus, Richards teaches that the effect of mutation on protein stability, a prerequisite for biological function, is unpredictable. Richards also teaches that even limited amino acid modifications can have dramatic effects on protein structure and function. In the second column on page 791, Richards cites the example of influenza virus hemagglutinin protein, wherein alterations in the ionization state of just a few ionizable groups dramatically alters the biological behavior of the molecule. Citing a published study of done on the gene V protein, Richards teaches that, in spite of only limited modification at two amino acid positions, "[t]he effects on the overall stability of the protein were remarkably variable" (page 794, column 1). In the paragraph bridging pages 796 and 797, Richards teaches,"[i]n single site mutants, the structural changes are generally greatest near the site of mutation, and moving away, decrease radially in all directions. *Even the small changes are so complex that the linkage relations do not allow assignments of the energetic changes to unique*

*parts of the altered residue and its immediate contacts*" (emphasis added) and "[t]here is no convincing explanation yet of how the changes in binding can produce a major movement over such a distance." Finally, in the first full paragraph in the second column on page 793, Richards teaches, "[a]lmost all mutations are accompanied by some conformational change, making prediction of the effects on stability difficult. *In most cases mutations lead to lowering of the stability*." (emphasis added). Thus, Richards teaches that small changes in the primary structure of a protein frequently have dramatic effects on the higher order structure and function of the protein, and that these effects are highly unpredictable. Given these teachings, the skilled artisan would understand that most of the polypeptides encompassed by the genus of all structural variants of porcine CAR would not have the recited function of mediating adenoviral transduction.

The prior art, exemplified by Fechner *et al.* (*supra*), also describes several species homologues of nucleic acids encoding CAR proteins which are highly conserved. However, the art does not set forth the structural requirements for mediating adenoviral transduction such that the skilled artisan would be able to identify those variants having the recited function without resorting to blind trial and error experimentation to make and test each and every possible variant.

*Amount of direction provided by the inventor and existence of working examples*: As described above, the specification provides a single example of a polypeptide having the recited function. Beyond that, the specification provides only general guidance as to how the variants should be constructed (see especially page 5, first full paragraph) and describes how variants can be tested for function (see especially Example 3). The teachings of the specification do not,

however, address the art recognized unpredictability of the effect of amino acid substitution on protein function. Thus, the skilled artisan seeking to make the full scope of the claimed invention would have to resort to blind trial and error experimentation to make and test each variant to identify those variants encompassed by the claims.

*Relative skill of those in the art and quantity of experimentation needed to make or use the invention*: Although the relative level of skill in the art is high, the structural limitations set forth in the claims encompass a large genus of nucleic acid molecules of disparate structure, most of which would not have the recited function. Although the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim non-enabled (*Atlas Powder Co. v. E.I. du Pont de Nemours & Co* (224 USPQ 409, 414; hereinafter *Atlas*), *Atlas* also provides, "[o]f course, if the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims might indeed be invalid" (page 414). In the instant case, the claims encompass an enormous number of embodiments, the vast majority of which would be inoperative. Furthermore, the art teaches that it is not possible to predict which embodiments would be operative or inoperative without engaging in empirical experimentation to test each and every embodiment. Therefore, determining which embodiments that were conceived, but not yet made, would be inoperative or operative would clearly require expenditure of more effort than is considered routine in the art. Therefore, the disclosure is enabling only for a nucleic acid encoding the porcine CAR set forth as SEQ ID NO: 2 and fragments thereof.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 8-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite in being directed to "Host cells". First, because the phrase is not preceded by a definite or indefinite article it is not clear whether the claim is directed to specific host cells (i.e., the host cells) or generic host cells (i.e., a host cells). Amending the claims to include an appropriate article would obviate this ground for rejection. Further, the use of the plural "host cells" is confusing because it is not clear whether Applicant is claiming a mixed population of cells, or whether the claim is perhaps limited only to a plurality of cells and excludes single cells. Use of the singular is recommended if applicant intends that the claim encompass any cell comprising the identified vector regardless of whether that cell is found alone, or within a plurality or mixed population.

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 3 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Fechner *et al.* (*supra*).

Fechner *et al.* teaches various polypeptides which mediate adenoviral transduction (i.e., CAR proteins from human, mouse, rat, dog and pig; see especially Figure 4). In the caption to Figure 4, Fechner *et al.* also provides Accession numbers for nucleic acids encoding each of the polypeptides disclosed in the Figure. At least to the extent that the claims encompass nucleic acids encoding variants, which include substitutions, additions, deletions, fusions and truncations (specification page 6, line 1-2) of the porcine polypeptide disclosed in the instant application, the nucleic acids disclosed by Fechner *et al.* anticipate the subject matter of claims 3 and 4. Thus, the claims are unpatentable over Fechner *et al.*

Claims 3-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Tomko *et al.* (WO 98/33819).

Tomko *et al.* teaches nucleic acids encoding polypeptides which mediate adenoviral transduction (i.e., CAR proteins from human and mouse; see especially SEQ ID NO: 1 and 3). At least to the extent that the claims encompass nucleic acids encoding variants, which include substitutions, additions, deletions, fusions and truncations (*Id.*) of the porcine polypeptide disclosed in the instant application, the nucleic acids disclosed by Tomko *et al.* anticipate the subject matter of claims 3 and 4.

Tomko *et al.* further teaches vectors and plasmids comprising the disclosed nucleic acids, according to claims 5-7, and host cells comprising said plasmid vectors, according to claims 8-10 (see especially beginning the first full paragraph on page 34 and continuing through the first full paragraph on page 35).

The nucleic acid, vector and host cell taught by Tomko *et al.* are the same as those claimed in the instant application; therefore, the limitations of the claims are met by Tomko *et al.*

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section. 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 3-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fechner *et al.* as applied to claims 3 and 4 above and further in view of Tomko *et al.*

As described above, Fechner *et al.* teaches nucleic acids encoding various polypeptides which mediate adenoviral transduction. Fechner *et al.* does not teach plasmids, vectors or host cells comprising said nucleic acids.

Tomko *et al.* teaches expression or recombinant CAR proteins by inserting DNA encoding CAR proteins into expression vectors and introducing the expression vector into a host cell (see especially the first full paragraph on page 35). It would have been obvious to one of ordinary skill in the art at the time the invention was made to construct an expression vector and host cell comprising the nucleic acids of Fechner *et al.* according to the teachings of Tomko *et al.* in order to express recombinant CAR proteins.

Motivation to combine these teachings comes from Tomko *et al.* who teaches a variety of uses for the recombinant protein; particularly to raise antibodies which can be used in quantitative or qualitative assays for CAR proteins (page 39, second full paragraph), including diagnostics. Absent evidence to the contrary, one would have a reasonable expectation of success in combining these teachings because recombinant protein expression is routine in the art and Tomko *et al.* demonstrates successful heterologous expression of two CARs (see especially Example III). Thus, the claimed invention as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

dms
August 13, 2003

REMY YUCEL, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600